CLINICAL STUDY

Impact of hepatitis B core antibody (anti HBc) seropositivity on interferon/ribavirin treatment response in patients with chronic hepatitis C

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Abstract

AntiHBc seropositivity among patients with chronic HCV infection is not a rare entity (57.14 %). We observed that antiHBc antibody seropositivity does not have a significant impact on treatment responses to interferon/ribavirin therapy in patients for chronic HCV infection in contrast to some reports in the literature *(Tab. 6, Ref. 39)* Full Text (Free, PDF) *www.bmj.sk*.
Key words: hepatitis B, antibody, antiHBc-seropositivity, interferon, ribavirin, chronic hepatitis C.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are leading causes of chronic liver disease worldwide, including chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Both agents are transmitted parenterally and share common routes of infection. In regions where HCV infection is widespread, prevalence of HBV infection is also reported as high (6–8), and consequently multiple HBV and HCV infection is frequent and is generally found to be associated with more severe liver damage (9–11). Coinfection with HBV among patients with chronic HCV infection in the absence of serological markers for HBV (also called occult HBV infection, defined by the presence of HBV DNA in the absence of detectable HBsAg in serum) is found at frequency of approximately 50 %– 87 % (12–15). In such patients, this occult HBV infection may be associated with more severe liver damage and even the development of hepatocellular carcinoma (16–21). Co-infection with HCV may downregulate or suppress HBV replication (22–24). Additionally, it has been reported that the response to interferon treatment is lower in patient with chronic HCV infection having occult HBV infection than cases without HBV infection (25–27). Zignego et al stated that decline in treatment response is due to occult HBV infection (26, 27). Several studies have also suggested that occult HBV infection may correlate with a lack of response to interferon treatment in patients with chronic hepatitis C. Thus, we performed this study to assess the frequency and clinical consequences of occult HBV infection in chronic hepatitis C patients undergoing interferon/ribavirine therapy.

Patients and methods

Thirty eight patients (20 female, 18 male) with naive chronic hepatitis C infection having elevated ALT, detectable serum HCV RNA followed in Turkiye Yuksek Ihtisas Hospital, Gastroenterology Clinic beween January 1999 and September 2002 were enrolled in the study. Complete blood count, liver function tests (ALT, AST), serum HCV RNA PCR and HBV DNA PCR, viral hepatitis serology, autoimmunity markers (AMA, anti-LKM-1, ASMA), serum iron indexes were evaluated in all paients. Three paients were dropped from the study due to side effects and lack of cooperation. Liver biopsy was performed in 33 patients. One patient did not accept liver biopsy, the other had borderline thrombocytopenia. Liver histopathological examination were determined according to Knodell histological activity index (HAI) as follows; normal if HAI<2, mild hepatitis if HAI between 3–6, moderate hepatitis if HAI between 7–11, severe hepatitis if HAI>12 (28). Fibrosis was determined as follows: 1 (no fibrosis), 2 (mild fibrosis), 3 (moderate fibrosis), 4 (cirrhosis). Study

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Tab. 1. Patient characteristics before treatment.

Gender	Female n=18 (51.4 %)	Male n=17 (48.6 %)
Age	51.6±1.75	
Patient number underwent liver biopsy	33	
Mean HAI value	9.2±3.3	
Mean Fibrosis Score	1.3±1	
Mild HAI (HAI:3-6)	8/33 (24.2 %)	
Moderate HAI (HAI:7-11)	15/33 (24.2 %)	
Severe HAI (HAI>12)	10/33 (30.3 %)	
HBc IgG(+) cases	20 patients (57.1 %)	
HBc IgG(-) cases	15 patients (42.9 %)	
Anti HBs(+) cases	15 patients (42.85 %)	
Anti HBe(+) cases	10 patients (28.57 %)	
Serum detectable HBV DNA PCR	3 patients (8.5 %)	

exclusion criterias were as follows: active hepatitis B infection, autoimmune disease, alcoholic liver disease, metabolic disease, HIV positive patients, white blood cell count <2.000/mm^3 or thrombocytes count <50.000/mm^3, presence of decompansated cirrhosis, age <18 or >75 years. Patients were given IFN •2b, 3 MU/3 times in a week subcutaneously and Ribavirin (RIBA) 1000–1200 mg/day orally for 12 months. Patients were followed by monthly blood count and liver enzyme evaluation. HCV RNA PCR was analysed at the beginning of therapy and 6th, 12th, 18th months. Patients were divided into two groups according to presence of occult HBV infection. Treatment response was defined as normal enzymes and undetectable HCV RNA PCR. Early response (ER) (6th months), end of treatment response (ETR) (12th months) and sustained response (SR) (18th months) were investigated. Relapse was defined in patients having response at the end of treatment but developing liver enzyme elevation and detectable HCV RNA PCR at 18th months. HCV RNA PCR was analysed via ABgene ROCHE one step RT PCR (Surrey, UK). Anti HCV was investigaed with ELISA III (ELISA, Abbot, Chicago). AST, ALT GGT, ALP were measured with Roche/Hitachi system (Roche Diagnostics GmbH Germany).

Tab. 3. Relationship of end of treatment and sustained response rates.

	Cases with sustained response	Cases without sustained response	Total
Cases with end of treatment response	12	6	18
Cases without end of treatment response	0	15	15
Total	12	21	33

PPV – 66.7 %, NPV – 100 %, sensitivity – 100 %, specificity – 71.4 %

Statistical analysis

Parametric values were compared with student's t-test and chi-square test. Nonparametric values were compared between the different groups of patient using non-parametric Spearman correlation. Results were considered statistically significant when the *p* value was (•0.05).

Results

Early, end of treatment and sustained response rates of all patients were 45.7 %, 57.15 % and 36.36 % respectively. The patient characteristics, demographic feaures, HAI and fibrosis scores, serological profiles were shown in Table 1. Mean pre-treatment HAI value of patients showing sustained response rate were lower than that of ones who did not have sustained response, but there was not statistically significant (7.9±2.5 versus 9.8±3.6, p=0.134). Accordingly, mean fibrosis scores of patients showing sustained response rate were significantly lower than that of ones who did not have sustained response (0.64±0.50 versus 1.0±1.0; p=0.001). AntiHBc antibody seropositivity did not have significant impact on treament response rates as shown Table 2 (p=0.26, p=0.18, p=0.76). But, interestingly sustained response rate was found to be lower in patients with occult HBV infection than the ones who did not have occult HBV infection (31.6 %

Tab. 2. Early response, end of treatment response and sustained response rates of paients with or without occult HBV infection.

	Early response n=35		End of treatment response n=35		Sustained response n=33	
	Responder n=16	Non-responder n=19	Responder n=20	Non-responder n=15	Responder n=21	Non-responder n=21
Anti HBc IgG seropositive n=20	7 35%	13 65%	9 45%	11 55%	6 31.6%	13 68.4%
Anti HBc IgG seronegative n=15	9 60%	6 40%	11 73.3%	4 26.4%	6 42.9%	8 57.1%
p	0.26		0.18		0.76	

Tab. 4. Transaminases levels of patients in relation with response rates.

	Pretreatment levels (0 month) n=35		Treatment levels (6 months) n=35		End of treatment levels (12 months) n=35		18th months levels n=33	
	AST U/L	ALT U/L	AST U/L	ALT U/L	AST U/L	ALT U/L	AST U/L	ALT U/L
Cases with end of treatment response	55±22	87±53	26±13	28±13	26±10	27±14	23±11	27±18
Cases without end of treatment response	82±37	105±60	47±25	44±21	50±34	51±35	60±26	66±33
p	*p=0.033	p=0.41	**p=0.003	*p=0.022	**p=0.007	**p=0.01	**p=0.001	**p=0.003

*p <0.05, **p< 0.01

Tab. 5. Pretreatment features of paients with and without occult HBV infection.

	Anti HBc IgG seropositive n=20		Anti HBc IgG seronegative n=15P		p
Gender	Male 11/20 (55%)	Female 9/20 (45%)	Male 6/15 (40%)	Female 9/15 (60%)	
Age	53.30		49.33		
Patients with detectable HBV	0		3		
DNA viral load Mean HAI score	9.9+3.4		8.3+3.1		=0.17
Mean FS	1.3+1.1		1.1+0.8		=0.25
AST (U/L)	83.8+37.36		58.33+25.69		=0.03
ALT (U/L)	115.25+67.85		76.27+27.04		=0.04
Anti HBs seropositive	1		23		
Anti HBs seropositive	8		12		
Anti HBe seropositive	9		1		
Anti HBe seronegative	11		14		

and 42.9 % respectively). Virological response rates of patients with anti-HBcIgG and without anti-HBcIG in 6th month were 55 % and 60 respectively. But it was not statistically significant (p=1). ETR predicted SR with 66.7 % positive predictive value (PPV), 100 % negative predictive value (NPV), 100% sensitivity and 71.4 % specificity (Tab. 3). Mean age of sustained responders was significantly lower than that of cases who did not show sustained response (45.2±12.8 versus 55.3±10.1; p= 0.018). 8 of 18 patients whose HCV RNA loss were observed, showed sustained response. 4 of 15 (26.7 %) patients whose HCV RNA load continued to be detectable showed sustained response. HCV RNA loss at 6th month of treatment did not effect the sustained response rate (p=0.488). Pretreatment AST levels were siginificantly lower in sustained responders than those of cases non-responders (55±22 U/L versus 82±38 U/L, p=0.033). That siginificance was not seen in ALT levels. 6th months, 12th months and 18th months AST and ALT levels of sustained responders were significantly lower thant those of cases who did not show sustained response (p=0.003 and p=0.022, p=0.007 and p=0.011, p=0.001, p=0.003, respectively) (Tab. 4). Pretreatment HAI and fibrosis scores were not found to be significantly different between patients who were seropositive or seronegative for anti HBc IgG (p=0.17, p=0.25) (Tab. 5). There was a moderate degree correlation between 6th and 12th months response (r=0.679, p<0.001). Similarly, a moderate degree correlation was also observed between 6th months and 18th months response (r=0.371, p=0.034). Between 12th months and 18 months response, a moderate degree correlation was also seen (r=0.69, p<0.001). SR was seen 66.6 % of patients with end of treament responders. Occult HBV infection did not have an impact on relapse rates (p=0.867) (Tab. 6). There was no significant difference on 6th months, 12th months and 18th months response rates of patients groups who were seropositive for anti HBs or seronegative (p=0.65, p=1, p=0.56). Accordingly, there was no significant difference on 6th months, 12th months and 18th months response rates of patients groups who were seropositive for anti HBe or seronegative (p=1, p=1, p=0.01) (Tab. 5).

Tab. 6. Occult HBV infection features of relapsers and non-relapsers.

	Relapsers	Non-relapsers	Total
Anti HBc IgG seronegative	6	4	10
Anti HBc IgG seropositive	6	2	8
Total	12	6	18

Discussion

Occult hepatitis B virus (HBV) infection is characterized by the presence of HBV DNA in the absence of hepatitis B surface antigen (HBsAg) in the patient serum (1–5). Several possibilities have been hypothesized as the mechanisms of occult HBV infections. These include: 1) mutations in the a determinant of the Surface gene that interfere with the recognition of HBsAg by antibodies (29–34). 2) HBsAg is not detectable by standard enzyme immunoassay techniques, because of the presence of circulating immune complexes between HBsAg and anti-HBs, which can prevent the detection of both the antigen and the antibody (35); 3) co-infection with HCV may down-regulate or suppress HBV replication (22–24). Coinfection with HBV among patients with chronic HCV infection in the absence of serological markers for HBV (also called occult HBV infection, defined by the presence of HBV DNA in the absence of detectable HBsAg in serum) is found at a frequency of approximately 50 %–87 % (9, 12–15). In such patients, this occult HBV infection may be associated with more severe liver damage (36–39) and even the development of hepatocellular carcinoma (20–21). Co-infection with HCV may down-regulate or suppress HBV replication. Additionally, it has been reported that the response to interferon treatment is lower in patient with chronic HCV infection having occult HBV infection than cases without HBV infection (25–27, 38). Zignego et al stated that decline in response to interferon treatment is due to occult HBV infection. Several studies have also suggested that occult HBV infection may correlate with a lack of response to interferon treatment in patients with chronic hepatitis C. Accordingly, Cacciola et al reported similar results in a study with a larger patient group. They stated that chronic HCV infected patients that were seropositive for antiHBcIgG and seronegative for HbsAg had high rates of HBV DNA in liver tissues (46 %),and these patients with occult HBV infection responded to interferon treatment less than the patients without occult HBV (38). We performed this study to assess the frequency and clinical consequences of antiHBc seropositivity in chronic hepatitis C infected patients undergoing interferon/ribavirine therapy. Our results were somehow different from those of Cacciola et al. We founded that sustained response rates in patients with and without occult HBV infection were 31.6 % and 42.9 %, respectively ($p>0.05$). ER, ETR rates were not found significantly different between patient groups with or without occult HBV infection, either ($p=0.76$ and 0.26). Coinfection with HBV among patients with chronic HCV infection in the absence of serological markers for HBV is found at a frequency of approximately 50 %–87 % in the literature. Our rates were 57.1 % (HBs Ag seronegative/ /AntiHBc seropositive) and 42.9 % (HBs Ag seronegative/AntiHBc seronegative). This rates were similar with the world literature.

It has been reported that the response to interferon treatment is lower in patient with chronic HCV infection having occult HBV infection than cases without HBV infection. Sagnelli et al reported that severe liver damage was more frequent in patient group with occult HBV infection than patients without occult HBV infection (71.1 % versus 40.8 %, respectively, $p<0.005$) (36). Fukuda et al also stated similar results such that 52.3 % of HCV infected patients were associated with occult HBV and these cases had high HAI scores compared to patients without occult HBV37. Additionally, Cacciola et al. suggested that cirrhosis was more frequent in HCV infected (HbsAg seronegative) patients having detectable serum HBV DNA viral load (38). De Maria et al similarly reported higher cirrhosis rates more severe liver disease in HCV infected patients having occult HBV infection than ones that were seronegative for antiHBcIgG seronegative (32 % versus 22 %, $p<0.05$) (39). In our study, mean pretreatment HAI score was 9.21±3.31 and mean fibrosis score was 1.3±0.98. Eight patients (24.2 %) had mild degree, 15 patients (45.4 %) had moderate degree, 10 patients (30.3 %) had severe degree of liver histopathological findings. Even though there was not a significant difference, patients that were seropositive for antiHBcIgG had higher HAI and fibrosis scores than ones seronegative (9.8±3.4 and 1.4±1, 8.2±3 and 1±0.8, respectively, $p>0.05$). Only 3/35 (8.5 %) patients had HBV DNA PCR positive, and interestingly all three patients were seronegative for hepatitis B serology. This rate was different than that of Cacciola et al. But, Cacciola et al studied very sensitive PCR technique (4 different sequences including S, core and X protein were analysed). Sensitivity of technique plays important role in detection of DNA.

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